

REMARKS

Upon entry of the foregoing amendments, claims 1, 5-9, 29 and 32-36 are pending in the application. Claims 1 and 29 have been amended, and claims 3, 4, 30 and 31 have been canceled, to clarify the inventive subject matter and bring the claims into condition for allowance. Basis for the amendments to claims 1 and 29 may be found in the specification on page 4, lines 4-12; page 5, lines 6-9; and page 6, lines 9-16.

Applicants submit that the amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of Claims 1, 3-9 and 29-36 under
35 U.S.C. § 112, 2nd Paragraph

The Office Action states that claims 1, 3-9 and 29-36 are rejected under 35 U.S.C. § 112, second paragraph for the following reasons:

Claims 1, 3-9 and 29-36 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The phrase "average molecular weight" is vague and indefinite since for high polymers such descriptive language renders the claim indefinite absent an indication on how the average molecular weight was determined such as by number average molecular weight, weight average molecular weight and the like.

With regard to a § 112, second paragraph rejection, case law has defined two requirements under the statute: (1) that the applicant states the invention as something elsewhere in the

application which would fall within the scope of the claims; and (2) that the claims are communicated with a reasonable degree of particularity and distinctness to a person skilled in the art in light of the content of the disclosure and the teachings of the prior art. MPEP § 2171, § 2173, and § 2173.02.

Applicants submit that the foregoing amendments to claims 1 and 29 obviate this rejection. Claims 1 and 29 have been amended to remove the terminology "average molecular weight" to remedy the indefiniteness noted by the Examiner. Further, claims 3 and 30 have been canceled to remove the "average molecular weight" limitation from all of the pending claims. The recitation of an "average molecular weight" for the negative charged polymer constituted only one embodiment of the present invention and did not constitute a limitation which was critical to the invention. See Specification, page 4, lines 2-24.

Accordingly, the claims, as amended, do reasonably apprise persons of ordinary skill in the art of the invention's scope. Therefore, applicants respectfully request that the Examiner reconsider and withdraw the rejections.

2. Rejection of Claims 1, 3-9 and 29-36
under 35 U.S.C. § 103(a)

The Office Action states that claims 1, 3-9 and 29-36 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Leshchiner et al. for the following reasons:

This rejection is maintained for reasons stated already of record in the last Office action mailed as of January 16, 1998 as set forth on pages 7 and 8.

Applicants' arguments filed March 12, 1998 have been fully considered but they are not deemed to be persuasive.

Applicants traverse, arguing that the prior art does not render the instant claims prima facie obvious because applicants' invention is directed to achieving transdermal sustained release drug delivery and that applicants' claims are narrowly defined with respect to the negative charged to nonionic charged polymers. Moreover, applicants assert that the two phase matrix in the prior art is different from the instant polymer mixture. These arguments are respectfully traversed since applicants have provided mere argument without any supporting facts. Argument of counsel does not take the place of evidence on the record. Arguments of counsel are not evidence unless they are an admission. It remains the position of the Examiner that the instant claims are rendered prima facie obvious since all limitations of the claims have been met by the reference applied against the instant claims and it is not necessary for an inherent property or characteristic to be recited in the reference when the overall structure of the compositions in the reference is the same as those claimed.

Applicants argue that the instant invention achieves unexpected results vis-a-vis the prior art. This argument is respectfully traversed for the reasons that arguments of counsel cannot take the place of evidence on the record and that applicants have provided no proof that the claimed inventions achieve any unexpected results vis-a-vis the disclosure of '724. Accordingly, the instant case of prima facie obviousness has been maintained.

In response to the Examiner's rejection under 35 U.S.C. § 103(a), applicants respectfully provide the following traverse.

A. The present inventive subject matter

Applicants' claims as presently amended are directed to a composition comprising a stable, gelled polymer matrix. Significantly, the claimed composition is applied topically, is storage stable and provides sustained release of the therapeutic drug across the dermal barrier (i.e., transdermal drug delivery).

The polymer matrix consists of a negative charged polymer and a nonionic polymer combined in approximately equal amounts. This system is specifically designed to provide transdermal delivery of effective levels of drugs for a prolonged period of time, as well as exhibit storage stability and the ability to be applied topically. To achieve these desired properties, the claimed ratio between the negative charged polymer and the nonionic polymer is critical. See Specification, page 5, lines 21-31. Moreover, it has been determined that it is critical that sodium hyaluronate be used as the negative charged polymer. See Declaration, ¶¶ 6, 7 and 10.

The ability to achieve a storage stable gel capable of sustained release of a therapeutic drug by employing compositions with a relatively equal ratio of negatively charged polymer(s) to nonionic polymer(s) is entirely new and unexpected. It has been found that compositions with molar ratios outside the claimed boundaries develop various defects, such as air pockets and separation of the polymers, compromising the stability of the compositions, inhibiting their ability to sustain a long acting

release of a therapeutic drug and/or prevent transdermal delivery or topical application. Specification, page 5, lines 25-31. It has also been unexpectedly discovered that the use of sodium hyaluronate as the negatively charged polymer is critical in aiding in the dispersion of the matrix, further providing desirable stability to enable a preparation suitable for topical application. Specification, page 5, lines 32-34.

B. The cited reference

In contrast, Leshchiner et al. disclose biocompatible viscoelastic gel slurries having two phases, wherein the presence of a crosslinked polymer is required. See column 3, lines 23-35. Specifically, the crosslinked polymer is a highly modified hyaluronic acid derivative produced by a complex process which involves crosslinking using vinyl sulfone. See Examples 1-21. Further, Leshchiner et al. emphasize the rheological properties for the crosslinked polymer of gel slurries.

Leshchiner et al. do not disclose stable, gelled compositions or any manner of achieving transdermal, sustained release drug delivery. Further, Leshchiner do not appear to specifically disclose the use of sodium hyaluronate or topical administration.

C. A prima facie case of obviousness has not been established by the U.S. Patent and Trademark Office

Applicants respectfully submit that a prima facie case for obviousness has not been established in view of the substantial

differences between the presently claimed subject matter and the cited reference, Leshchiner et al. as clarified by the amendments to claims 1 and 29. In particular, the claims have been limited to compositions which contain sodium hyaluronate and provide transdermal drug delivery after topical administration. Applicants specifically direct the Examiner's attention to the following structural and functional distinctions between the presently claimed subject matter and the cited reference.

1. Claimed compositions provide topical gel preparations capable of transdermal drug delivery

The foregoing amendments to the claims clarify that the presently claimed subject matter is limited to compositions which are capable of topical administration and/or transdermal drug delivery. In contrast, Leshchiner et al. do not even address topical administration, transdermal drug delivery or sustained release transdermal drug delivery. Both transdermal sustained release drug delivery and a topical gel formulation are attainable because of applicants' discovery that the polymer ratio ranges to which the inventive subject matter is limited unexpectedly allow for same. By limiting the present invention to said polymer ratio ranges, the compositions described by Leshchiner et al. are nonobvious with regard to the particular purposes for which the compositions of the present invention are used (i.e., topical application or transdermal drug delivery). Formulations prepared in accordance with Leshchiner et al. would not be suitable for topical application. See Attached Declaration.

Even if certain compositions disclosed by Leshchiner et al. were to overlap the polymer ratio ranges of the present inventive subject matter, although applicants maintain they do not, the failure of Leshchiner et al. to recognize the significance of the ratio of negative charged polymers to nonionic polymers, for the purpose of providing a topical gel formulation, represents a nonobvious disclosure. The advantages, properties, utilities, and unexpected results flowing from the claimed invention are part of the invention as a whole and must be considered in the determination of obviousness. In re Chupp, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987). Consequently, it would not have been obvious to one of ordinary skill in the art to use the compositions disclosed by Leshchiner et al., or variations of same, to achieve a stable, gelled composition suitable for topical application and/or transdermal drug delivery where the disclosure did not suggest that a composition with such properties could be achieved. This is particularly true in view of the highly unpredictable nature of the chemical arts as recognized by extensive case law on the subject.

2. Claimed compositions require sodium hyaluronate

In addition to limiting the claims to compositions which are suitable for topical application, the foregoing amendments also limit the claims to compositions requiring the presence of sodium hyaluronate. The specific negative charged polymers to which the amended claims are limited represent an essential element in

achieving both stability and even dispersion of a drug throughout the polymer matrix. Stability is necessary for topical gels and even dispersion of drug throughout the polymer matrix is necessary for achieving a transdermal sustained release of drug. The disclosure of Leshchiner et al. is deficient in its failure to address the issue of achieving a stable gel and even dispersion of drug throughout a polymer composition. Moreover, Leshchiner et al. does not appear to specifically disclose sodium hyaluronate as a component of the described slurries.

3. Claimed compositions are stable and applied topically

The present invention is limited to stable gels suitable for topical application. Stability is achieved through the presence of the negative charge limitation (i.e., sodium hyaluronate) and the polymer ratio ranges to which the invention is limited. In contrast, Leshchiner et al. disclose compositions which would be unstable and exhibit the polymer shearing effect which produces unacceptable turbulence and air pockets in said compositions with resulting loss of potency and efficacy. See Specification, page 5, lines 25-31. Moreover, Leshchiner et al. teach a gel slurry where the polymer is suspended in an aqueous phase that may or may not be another polymer, whereas the applicants' inventive subject matter is specifically limited to a mixture of polymers and not a slurry (i.e., a thin watery suspension). The unstable slurries disclosed by Leshchiner et al. are not only absent in applicants' inventive subject matter, but would be completely inappropriate for the

applicants' claimed inventive subject matter which requires a stable, gelled polymer mixture suitable for topical application.

In view of the substantial structural and functional distinctions described above, applicants' respectfully submit that the claimed composition is not disclosed or suggested by Leshchiner et al. By disclosing slurries not dependent on the molar ratio of negative charged polymer to nonionic polymer, Leshchiner et al. fail to appreciate both the unexpected properties of using equal mixtures of nonionic and negative charged polymers, as claimed by applicants. Moreover, by failing to specifically disclose sodium hyaluronate, Leshchiner et al. fail to recognize the significance of sodium hyaluronate for attaining a composition suitable for topical application and transdermal drug delivery. Leshchiner et al. do not recognize the advantageous properties of a polymer mixture which is not a two phase suspension, or the usefulness of a specific polymer mixture unexpectedly found to store and release therapeutic drugs efficiently, efficaciously and transdermally, over prolonged periods of time. In failing to appreciate their advantages, Leshchiner et al. provide no reason or incentive for using the polymer matrix claimed by applicants.

By teaching the use of crosslinked polymers and carboxymethyl cellulose, not only does the cited reference fail to provide the present inventive subject matter, but it teaches away from applicants' inventive subject matter because both elements are unsuitable for transdermal drug delivery. Moreover, the emphasis

by Leshchiner et al. on the rheological properties of gel slurries also teaches away from the presently claimed subject matter because said properties are not relevant to producing a composition capable of sustained release transdermal drug delivery. The above teachings by Leshchiner would tend to lead a person of ordinary skill in the art away from the direction of the presently claimed subject matter which excludes crosslinked polymers and carboxymethyl cellulose.

It is readily apparent that there is no disclosure of facts in the prior art which support a legal conclusion that the claimed invention was obvious at the time it was made. It is a well settled principle that prior patents are references only for what they clearly disclose or suggest and that it is not proper to use a patent as a reference when its structure is modified to one which the reference does not suggest. Further, where there is no teaching or suggestion to 'try' a particular combination, a prima facie case has not been made by the PTO. In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). It is improper to reject a claim when what might have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art either gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In re O'Farrell 7 USPQ2d 1673, 1681 (Fed.Cir. 1988). The fact that a claimed product is within the broad field of the

prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons for making such selection. Ex parte Kuhn, 132 USPQ 359 (POBA 1961). Under this standard it is readily apparent that the claimed technology is entirely unrelated to that which is disclosed by the cited reference.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. All of the facts must be considered and it is not realistic within the framework of Section 103 to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. Accordingly, withdrawal of the rejection and an allowance of claims 1, 5-9, 29 and 32-36 is respectfully requested.

D. Declaration under 37 C.F.R. § 1.132 by Alan Drizen rebuts prima facie case of obviousness asserted by Examiner

Even if a prima facie case of obviousness was found to exist, applicants respectfully submit that the attached Declaration under 37 C.F.R. § 1.132 by Alan Drizen constitutes evidence sufficient to rebut said prima facie case. As explained in the Declaration, Leshchiner et al. is entirely inoperable with regard to both topical application and transdermal drug delivery. In particular, the hyaluronic acid derivative disclosed by the cited reference is

a crosslinked polymer which is not suitable for transdermal drug delivery or topical formulations. See Declaration, ¶¶ 6, 7 and 8.

Further, the Declaration substantiates that the compositions disclosed in Leshchiner et al. are substantially different from the presently claimed compositions from both a structural and functional perspective. For example, Leshchiner et al. do not specifically disclose sodium hyaluronate as required by the present invention, and compositions prepared in accordance with the teachings of Leshchiner et al. would not be topical gels or gels capable of sustained release transdermal drug delivery subsequent to topical administration. See Declaration, ¶¶ 10 and 11.

Additionally, the Declaration provides documentation of the unexpectedly superior properties of the present inventive subject matter with regard to transdermal drug delivery. See Declaration, ¶ 13.

Accordingly, withdrawal of the rejection and an allowance of claims 1, 5-9, 29 and 32-36 is respectfully requested.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of the remaining claims, and allow all pending claims presented herein for

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reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcome to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES

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